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CHANCROID

DONOVANOSIS
(GRANULOMA INGUINALE)

LYMPHOGRANULOMA VENEREUM
(LGV)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
CENTERS FOR DISEASE CONTROL

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CHANCROID

DONOVANOSIS
(GRANULOMA INGUINALE)

LYMPHOGRANULOMA VENEREUM
(LGV)

Prepared by
Gavin Hart, M.D.

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Venereal Disease Control Division
Atlanta, Georgia 30333

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CHANCROID

Synonyms

Chancre mou; soft sore; soft chancre; ulcus molle.

Definition

Chancroid is a specific ulcerative genitoinfectious disease caused by *Haemophilus ducreyi,* a small gram-negative bacillus. Characteristic inguinal adenopathy often accompanies the genital lesion but systemic spread does not otherwise occur.

History. Chancroid was recognized as a clinical entity for centuries but was not differentiated from syphilis until 1852, by Bassereau. *Haemophilus ducreyi* was first isolated by Ducrey in 1889.

Infectious Agent

Haemophilus ducreyi is a fine, short (1-2μ) nonsporeforming nonacid-fast, gram-negative bacillus with rounded ends. In smears from primary lesions, it is most commonly observed singly or in small clusters along strands of mucus, whereas in bubo aspirate the organisms form no definite pattern.

H. ducreyi is fastidious but can be cultured on special media incorporating human or rabbit blood or blood products.[1] On culture the organism tends to form straight or tangled chains.

Epidemiology

The disease is most common in the Far East but occurs in most other countries. In white American troops in Korea, chancroid was 14 times as common as syphilis[2] (although syphilis is rare in most areas of the Far East), and in Vietnam it was second only to gonorrhea among venereal infections.[3] Among Australian troops in Vietnam, there were 163 cases among 1500 men in one year,[4] and a recent report[5] indicates a high prevalence in Rhodesia. The condition is probably overdiagnosed in the United States because the diagnosis is made by exclusion of other specific ulcerative conditions. This policy leads to the inclusion of nonspecific ulcers in this specific category. In Fiscal Year 1974 (July 1, 1973 to June

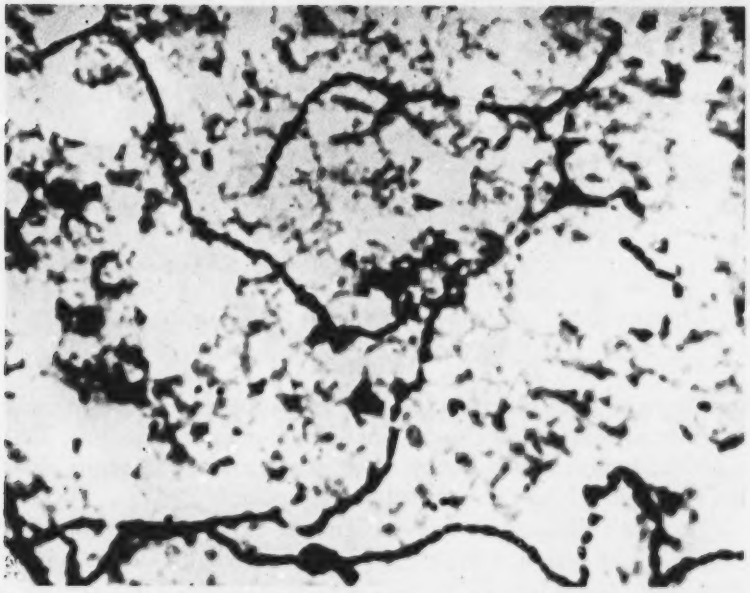

Fig. 1. Photomicrograph of spread from culture of *Hemophilus ducreyi.* Note chain formation of streptobacilli.

30, 1974), there were 1,064 cases reported in the United States, including 693 cases in nonwhite males.

Although chancroid is almost invariably transmitted by sexual contact, it is reported much less commonly in women, who usually constitute only 5-10% of the reported incidence. The reason for this phenomenon is unknown, but likely contributing factors include transmission by:

1. Female carriers without disease
2. Asymptomatic women with lesions of the vagina or cervix
3. Infected prostitutes who service large numbers of men. This may be the most significant factor since prostitutes provide the predominant promiscuous sexual outlet in the areas where chancroid is common.

Repeated reference to the relationship between chancroid and the poor, the socially unenlightened and the unhygienic is misleading. Individuals of any class or custom can acquire the disease if exposed to infection. Certainly it is not prevented by soap or washing, even when these measures are applied thoroughly immediately after intercourse.[4]

Chancroid is much more common in uncircumcised men.[2,3,4] The most macerated tissue beneath the prepuce results in break-

down of the normal integumental barrier to infection, and probably accounts for a higher incidence of infection in the uncircumcised. This probability is supported by the common sites of infection which suggest some form of traumatic prerequisite for invasion of the host. Lesions do occur in the circumcised, or at other sites such as the glans or penile shaft, but these are invariably more difficult to treat and possibly result from a more virulent organism or diminished host resistance.

Immunity

Infection offers no protection to the patient. Fresh lesions often occur by autoinoculation, and reinfection readily occurs immediately after cure.

Pathology

Lesions are usually confined to the genital sites most commonly traumatized during sexual contact: the internal surface of the prepuce and frenulum in the man and the labia, clitoris, fourchette and vestibule in the women. Pre-existing abrasions facilitate entry of the organisms.

A small papule surrounded by a zone of erythema first develops and soon erodes to produce a sharply circumscribed nonindurated ulcer with a granulating base. Multiple lesions may develop rapidly by autoinoculation, and suppurative adenitis of the inguinal lymph nodes is common in untreated cases. Systemic spread does not occur. Fusospirochetal superinfection may produce rapidly destructive lesions of the genitalia.

Histologically, the lesions show three layers.[6] The shallow, surface layer contains many polymorphs, red blood cells and debris; the wide midzone is edematous and shows endothelial proliferation of blood vessels but lack of fibroblastic repair; in the deep zone there is a dense infiltration of plasma cells and lymphocytes.

Symptoms

The incubation period is usually short, varying from 1 day to 14 days but averaging 4 to 5 days. The primary lesion begins as an inflamed macule which rapidly progresses to vesicular and pustular stages. It has usually eroded to leave a ragged ulcer by the time the patient presents for medical treatment. Up to 10 individual ulcers have been reported but usually there are only one or two.[2-4] When multiple ulcers occur, they usually vary markedly in size and shape. Individual lesions vary from 1 mm to 2 cm in diameter, averaging 0.5 cm, but confluent serpiginous ulceration of the coronal sulcus may encircle the penis.

Fig. 2. Chancroid. Ragged serpiginous ulceration of the coronal sulcus.

The chancroidal bubo is characteristic and may be a useful clue to the diagnosis. It occurs in 25-60% of cases, is usually unilateral, usually painful, unilocular and spherical with marked redness of the overlying skin. The inclusion of multiple disease states with a diagnosis of chancroid has probably contributed to reports of widely varying adenopathy in this condition, but bilateral adenopathy occasionally occurs. The inguinal adenitis usually appears within 7-10 days of the primary lesion; it softens, becomes fluctuant and may spontaneously rupture.

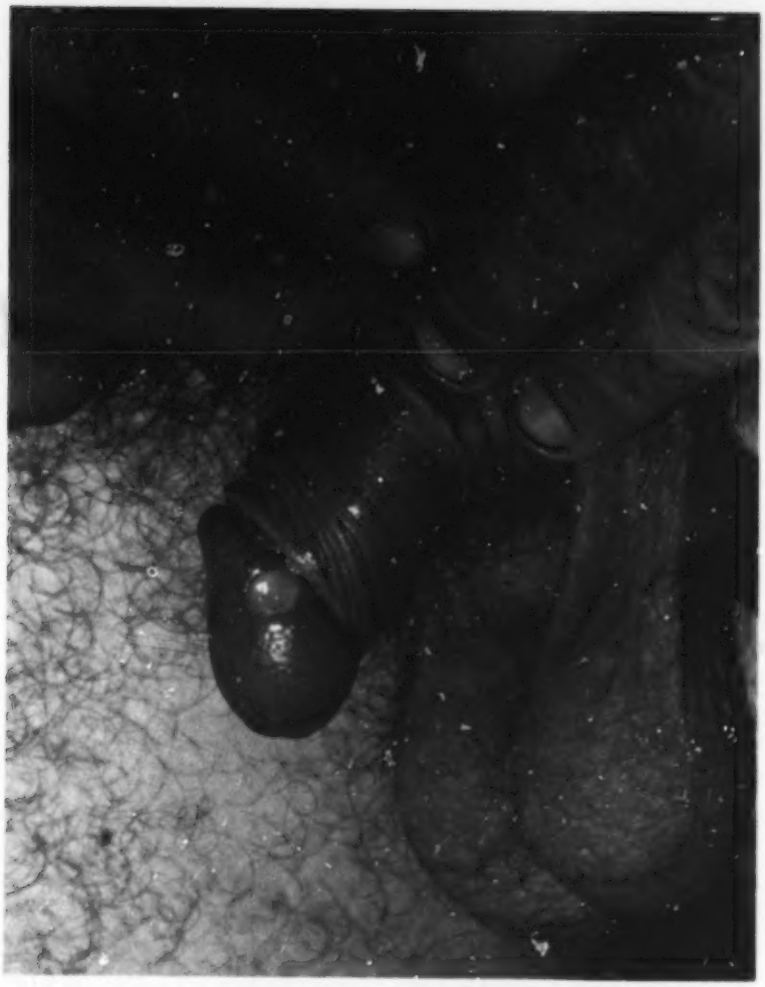

Fig. 3. Chancroid. Typical erosive lesion of the glans.

Clinical Varieties:

1. Usually one, but occasionally multiple, **shallow painful ulcers** surrounded by a broad erythematous halo generally occur on the deep surface of the prepuce. Diagnostic confusion with herpes genitalis may occur, but the lesions of herpes are usually more superficial, more numerous, of uniform size and surrounded by a narrower zone of erythema. Furthermore, the adenopathy associated with

Fig. 4. Giant chancroidal lesion in white male.

herpes is usually bilateral, tender and involves most of the superficial inguinal chain.

2. **Necrotic ulcers** with a ragged edge involving the coronal sulcus and coalescing to produce a ragged serpiginous gutter are virtually pathognomonic of chancroid. Such ulcers less commonly occur elsewhere on the penis.

3. Erosive lesions usually originate on the glans or shaft of the penis, occasionally at the preputial margin, and rapidly progress to produce widespread destruction of penile tissue.
4. Several other forms, such as transient chancroid, follicular chancroid, hypertropic chancroid and giant chancroid, have been described but are less common than the foregoing forms.
5. Extragenital chancroid lesions of the finger, tongue, lips, breast and eyelids have been reported but are uncommon.

Diagnosis

Identification of organisms from spreads or culture depends on adherence to specialized techniques.

1. Lesion Smears[7]

The lesion should be thoroughly cleaned with sterile saline and dried with gauze swabs. Serous exudate from the undermined border of the ulcer collected on a cotton-tipped applicator is carefully rolled (in one direction) onto a glass slide. This technique is essential to preserve the morphologic integrity of the organisms. Gram's stain is most frequently used, but Barritt's modification of Pappenheim's Pyronin Methyl Green Stain may be preferable.[8] With Barritt's modification, pus cells stain bluish green and bacteria, a brilliant red. Smears prepared from bubo aspirate may reveal typical gram negative coccobacilli as the sole flora, enabling conclusive diagnosis.

2. Culture.

The organism is fastidious and culture may not be warranted as routine diagnostic measures in some clinical settings but should be employed in environments where chancroid is seen commonly.

The organism is first isolated by inoculation in the serum surrounding a fresh clot (3 ml. of patient's or other human blood is used). Inactivation of serum at 56°C for 30 minutes is essential for the growth of laboratory strains, but may be omitted for clinical isolates.[1] The ulcers are cleaned as for preparation of smears and serous exudate is collected from the ulcer margin with a platinum loop. After 72 hours incubation at 35°C, growth is examined by stained smear and subculture onto Bacto-nutrient agar 1.5%, containing 5% human blood. After incubation in a candle jar at 35°C for 48 hours, *H. ducreyi* appear as slightly gray colonies 2-5 mm. in diameter with a rough surface texture.

The diagnosis of chancroid should only be made on positive grounds and the advice to make the diagnosis by exclusion is

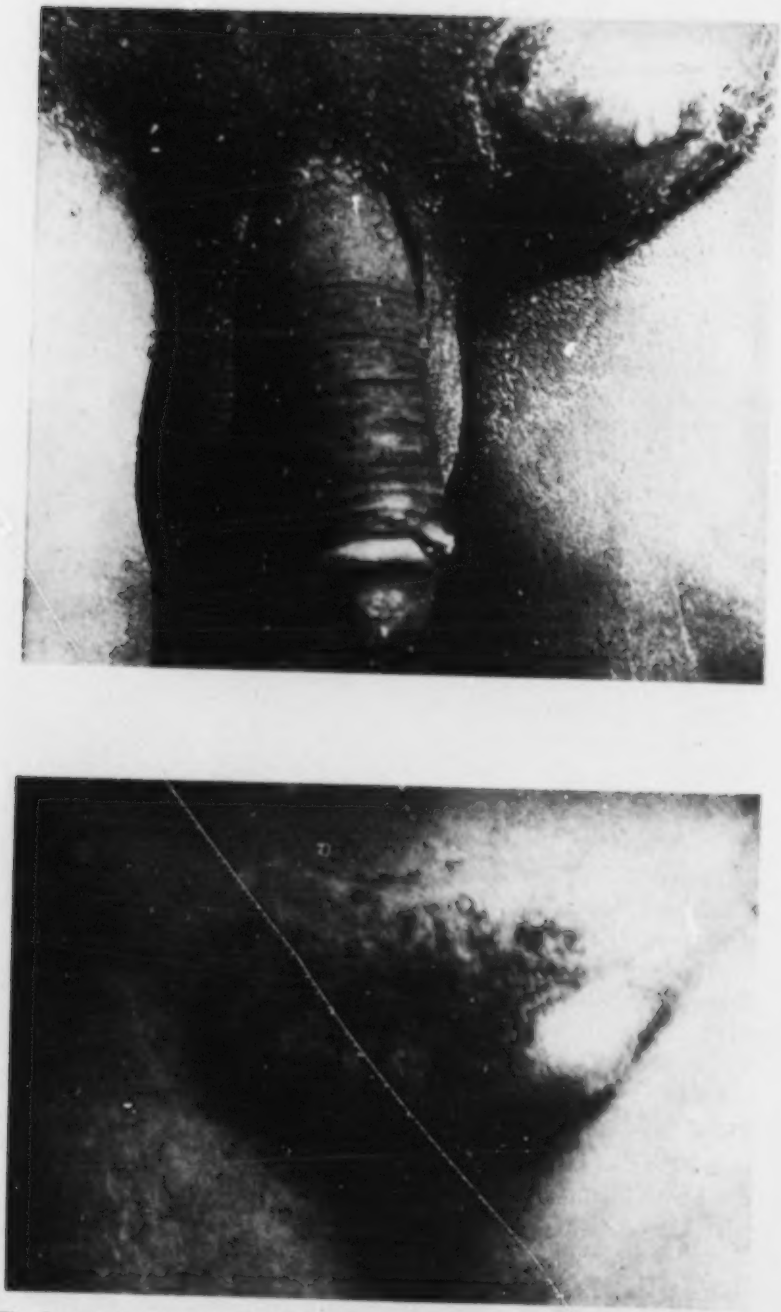

Fig. 5. Typical unilocular chancroidal buboes.

unsatisfactory since an array of nonspecific ulcerations will be included in this category and cause confusion. All cases resembling chancroid should be investigated for syphilis, since the two diseases may coexist. Diagnosis may be made on any one of the following criteria:

(1) Culture of the organism.

(2) Detection of organisms morphologically consistent with *H. ducreyi* as the sole organism in bubo aspirate.

(3) Tissue smears showing organisms resembling *H. ducreyi* in chains or clumps along strands of mucus. Observation of organisms consistent with *H. ducreyi* scattered among a diversity of other organisms is an inadequate criterion for diagnosis.

(4) A clinical presentation consistent with chancroid, plus any one of these features:
   a. Ragged serpiginous ulceration of the coronal sulcus
   b. Severely erosive lesions
   c. The classical unilateral bubo

Treatment

Oral sulfisoxazole (1 gm. every 6 hours for 10-14 days) is the treatment of choice. Tetracycline or tetracycline combined with sulfisoxazole has also been used effectively. However, in some areas, particularly S.E. Asia, resistance to these drugs now occurs.[4,9] These resistant cases should be treated with streptomycin or kanamycin (0.5 gm. twice daily for 10-14 days). These drugs should be used as first-choice treatment for erosive lesions and all chancroidal lesions in environments where more than 10% of cases are resistant to sulfisoxazole. Intravenous cephalothin (1 gm. 6 hourly) is usually effective for cases resistant to kanamycin.

Local therapy is a helpful adjunct for subpreputial ulcers. The prepuce should remain retracted throughout treatment and the ulcerative lesions cleaned three times daily with a suitable debriding solution. However, preputial retraction is contraindicated in the presence of preputial edema. Circumcision is contraindicated until the infection has subsided.

The bubo may be aspirated but should not be incised. Parenteral treatment soon after appearance of the primary penile lesion aborts the development of adenopathy, and uneventful resolution usually occurs if treatment begins before the inguinal mass becomes fluctuant. However, if therapy is delayed until signs of necrosis of the overlying inguinal skin appear, thorough aspiration is desirable, to avoid permanent scarring and deformity.

Prevention and Control

Soap and water have little prophylactic value against chancroid[4] but the condom, correctly used, is probably effective in most cases.

Since the consequences of the disease are closely related to delay in treatment, awareness of physicians and early treatment of detected cases are the main goals of any health program. If a large proportion of the disease is traced to a delineated group of prostitutes or other social group these should receive epidemiologic treatment.

Fig. 6. Autoinoculation. A drop of pus, aspirated from a chancroidal bubo in the right inguinal region (before breakdown of bubo), was injected subcutaneously into the left inguinal region, resulting in a typical chancroidal ulcer.

References

1. Deacon, W. E. et al.: V.D.R.L. Chancroid studies. 1. A simple procedure for the isolation and identification of *Hemophilus ducreyi*, J. Invest. Dermat. 26:407, 1956.
2. Asin, J: Chancroid, Amer. J. Syph. 36:483, 1952.
3. Kerber, R. E., Rowe, C. E. and Gilbert, K. R.: Treatment of Chancroid, Arch. Derm. 100: 604, 1969.
4. Hart, G.: The impact of prostitution on Australian troops at war. Unpublished doctoral thesis, University of Adelaide. South Australia. 1974.

5. Stamps, T. J.: Experience with doxycycline (vibramycin) in the treatment of Chancroid, J. Trop. Med. Hyg. 77:55, 1974.
6. Heyman, A., Beeson, P. B. and Sheldon, W. H.: Diagnosis of Chancroid, Amer. J. Path. 22:415, 1946.
7. Borchardt, K. A. and Hoke, A. W.: Simplified laboratory technique for diagnosis of Chancroid, Arch. Derm. 102:188, 1970.
8. Barritt, M. M.: An improved Pappenheim stain for detection of gonococci in smears of pus, Brit. Med. J. 1:254, 1943.
9. Marmar, J. L.: The management of resistant Chancroid in Vietnam, J. Urol. 107:807, 1972.

DONOVANOSIS
(Granuloma Inguinale)

Synonyms

Donavaniosis; granuloma contagiosa; granuloma Donovani; granuloma inguinale; granuloma inguinale tropicum; granuloma pudendi tropicum; granuloma venereum; sclerosing granuloma; ulcerating granuloma of the pudenda.

Definition

Donovanosis is a specific chronic granulomatous disease which usually affects the genitalia. The name granuloma inguinale, though widely used, is inappropriate for this condition. "Granuloma" is a nonspecific term, and its use may cause confusion with lymphogranuloma venereum (LGV), although this confusion is more marked when the term "granuloma venereum" is used. "Inguinal" is inappropriate since the inguinal region is involved in only a minority of cases and is usually secondary to genital infection. Furthermore, the name "granuloma inguinale" is not recommended in either New Guinea or India, the two countries where the majority of infections are reported. "Donovanosis" is used in New Guinea and "granuloma Donovani" has been suggested in India.

History.

Donovanosis was probably first described by McLeod in 1882. The causative organism *Donovania* (currently *Calymmatobacterium) granulomatis,* was discovered by Donovan in 1905.

Infectious agent. The infectious agent is *Calymmatobacterium granulomatis,* a gram-negative bacterium measuring 1.5 microns by 0.7 microns. In tissue smears, the bacteria appear enclosed in vacuolar compartments in large histiocytic cells or occasionally in polymorphonuclear leukocytes or plasma cells.[1] The bacteria reproduce in multiple foci within these cells until the vacuole contains 20-30 organisms, which mature and are then liberated when the infected cell ruptures.

The organisms have a surrounding cell membrane and overlying cell wall and possess a sharply defined capsule when mature. Small filamentous projections, of the size of bacterial fimbriae or pili,

extend from the cell wall. Culture on the chick embryonic yolk sac has been reported.[2]

Epidemiology

Although rare in most western countries, only 51 cases being reported in the United States in Fiscal Year 1974 (July 1, 1973 to June 30, 1974), Donovanosis is very common in New Guinea, India, the Caribbean and many other tropical or subtropical environments. In West New Guinea, up to 25% of some populations were infected in the 1920s, and 23.5% of male patients attending one urban VD clinic in 1972 had Donovanosis.[3] In India, 5.3% of patients attending a venereal disease clinic had this disease.[4]

The role of sexual transmission is controversial. Goldberg[5] isolated an organism resembling *C. granulomatis* from rectal specimens of nondiseased patients and elicited a history of rectal coitus from 25% of patients at clinics where Donovanosis was commonly seen. He also demonstrated that 58% of women attending these clinics had common enteric bacteria in the vagina. From these observations, he postulated that the vagina is often infected by autoinoculation from the rectum, but clinical disease occurs after sexual or nonsexual trauma of infected sites. Also,

Fig. 7. Donovanosis. Typical beefy exuberant granulomatous lesion of the penis.

Fig. 8. Donovanosis. Typical lesion of the prepuce.

Fig. 9. Donovanosis. Slowly progressive ulceration of the glans and penis.

Fig. 10. Donovanosis. Typical subcutaneous granulomata of the penis and inguinal regions.

sexual transmission is possible when bacteria are transferred from the bowel or contaminated vagina even when no clinical lesions of Donovanosis are present. This theory is consistent with the frequent association of infection with homosexual behavior. Anal intercourse is closely associated with rectal lesions of passive homosexual patients and penile lesions in their active partners.[6]

Zigas[7] screened a New Guinea population and detected lesions in none of 108 children under 1 year, 4.4% of 318 children 1-4 years of age, none of 2,966 children from 5-14, and 4.9% of 6,594 persons over 15. Among infected individuals the male:female ratio was 1.4:1. He suggested that the young children were probably infected by sitting on the laps of diseased parents or relatives, whereas adult infection was associated with sexual intercourse.

The disease is reported more commonly in men, one study[4] demonstrating a male:female ratio of 2.3:1. In most cases, lesions cannot be detected in sexual contacts but a number of studies have detected infection in 12-52% of marital or steady sexual partners.[4] The disease is only mildly contagious and repeated exposure is apparently necessary for the development of most clinical cases.

The morbidity from Donovanosis depends on the attitudes and behavior among the groups in which it occurs. Possible improved

hygiene would reduce the prevalence of the disease, but certainly early treatment would make infection trivial. However, patients usually delay for months before seeking treatment, 73% in one study delaying for more than 2 months.[4] The high prevalence of other venereal infections in these patients merely reflects this duration of illness and the behavior of the host. It is to be expected that a large proportion of individuals who behave promiscuously in an infected population will acquire another venereal disease during the 2-6 months before they seek treatment for their Donovanosis. Scarring and other permanent structural damage from Donovanosis may hinder effective treatment of these coexisting diseases.

Pathology

The primary lesion begins as an indurated nodule which erodes to form a beefy exuberant granulomatous heaped ulcer. This usually progresses slowly, often coalescing with adjacent lesions or forming new lesions by autoinoculation, particularly in the perineal

Fig. 11. Extensive lesion and daughter lesions of granuloma inguinale, ulcerative type.

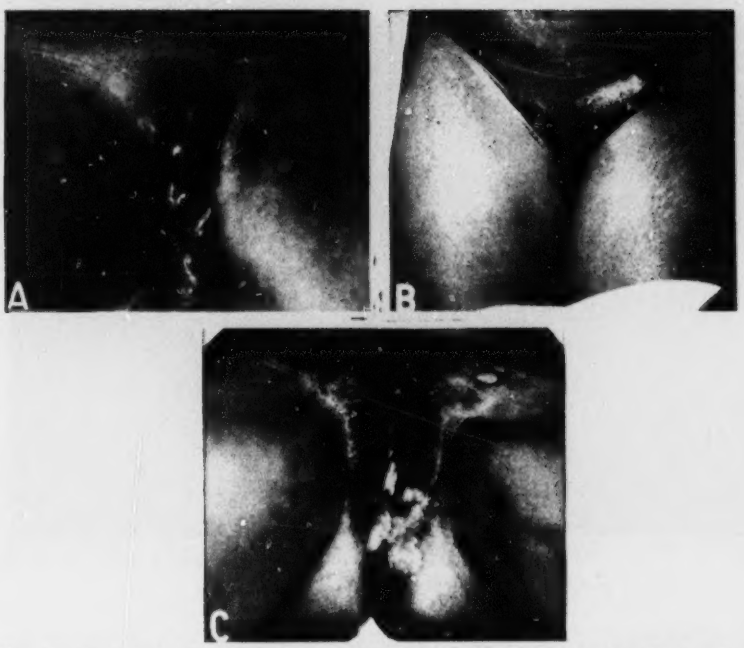

Fig. 12. Pseudobubo of granuloma inguinale. *A.* Granuloma inguinale of pudendum of 2 years' duration followed by inguinal pseudobubo. Note early bubolike induration in left inguinal region. *B.* Several weeks later the pseudobubo is fluctuant. *C.* Rupture of pseudobubo with typical inguinal granulomatous lesion.

region. Extensive acanthosis and dense dermal infiltrate, mainly plasma cells and histiocytes, occur. Some polymorphs are present in focal collections or scattered throughout the infiltrate, but lymphocytes are rare. The pronounced marginal epithelial proliferation may simulate early epitheliomatous change.

The infecting organisms invade mononuclear endothelial cells, and, when mature, feature metachromatic bars which stain blue or black with Wright's stain. The pathognomonic feature of Donovanosis is the large infected mononuclear cell, 25-90 microns in diameter, containing many intracytoplasmic cysts filled with deeply staining Donovan bodies.

Metastatic haematogenous spread to bones, joints and liver occasionally occurs. Occasionally, the lymphatics are involved but the frequent "suppurating bubo" of the groin is in fact a subcutaneous granuloma (pseudobubo). In chronic cases, healing with fibrosis occurs concurrently with tissue destruction caused by

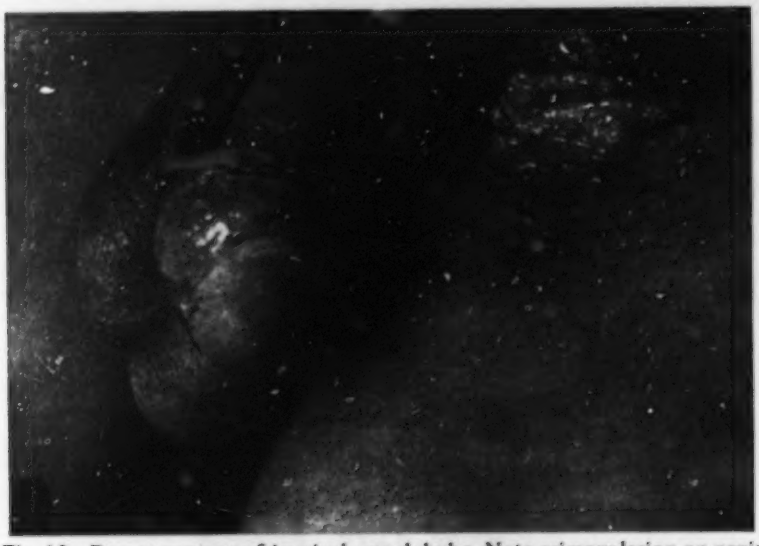

Fig. 13. Recent rupture of inguinal pseudobubo. Note primary lesion on penis which preceded it by several weeks.

the expanding lesion. Secondary infection often occurs, aggravating tissue destruction and residual scarring.

Symptoms

The incubation period is unknown but is probably 8-80 days. Subcutaneous injection of infected exudate into volunteers suggested an incubation period of 40-50 days, but Zigas[7] produced a lesion in himself within 9 days by introducing infected material into an abraded area of his thigh.

The disease begins as single or multiple subcutaneous nodules which erode through the skin to produce clean granulomatous, sharply defined lesions which are usually painless. These lesions which bleed readily on contact, slowly enlarge. Secondary infection may contribute to necrotic debris on an ulcer or at its margin, but sourrounding cellulitis rarely occurs. Contact with adjacent skin, particularly in the perineal or perianal region, frequently produces "kissing lesions." Fibrosis occurs concurrently with extension of the primary lesion and phimosis or lymphedema of distal tissues is common in the active phase of the disease.

Clinical Varieties:

1. Over 80% of cases demonstrate hypertrophic, vegetative

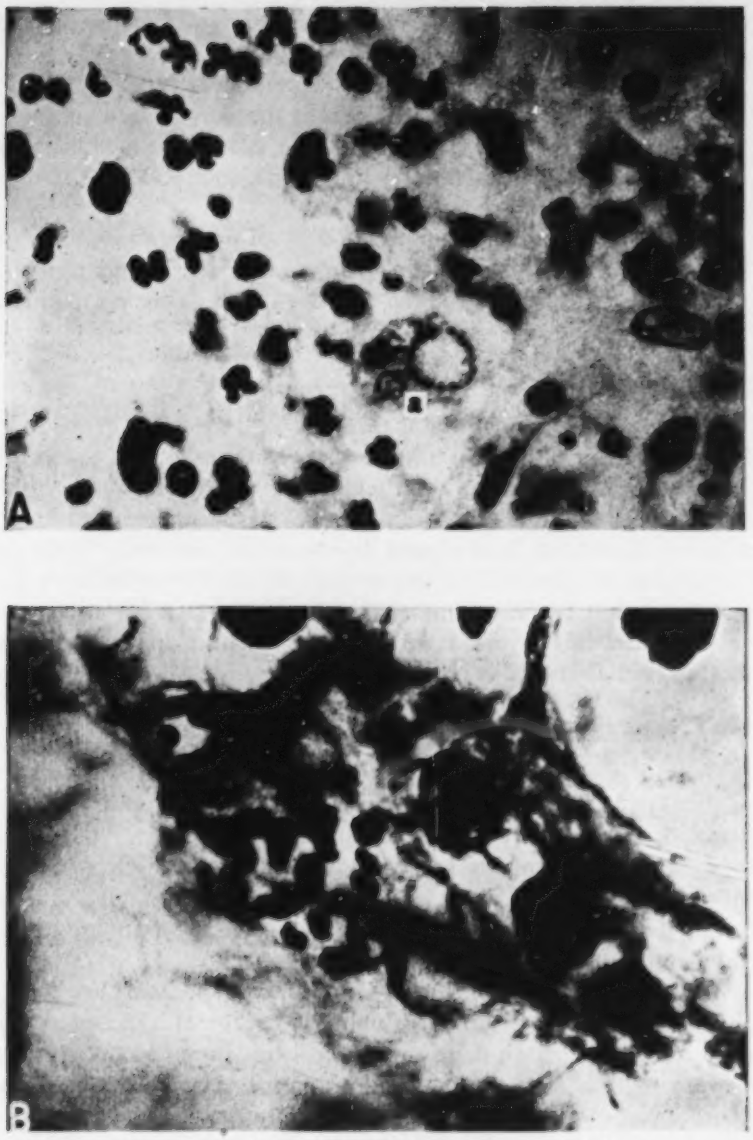

Fig. 14. *A.* The characteristic cellular response as observed in tissue section stained with Delafield's hematoxylin and eosin. a, the pathognomonic cell, is diagnostic of granuloma inguinale. Note the small rounded bodies lining the periphery of the intracytoplasmic cysts. *B.* A biopsy section stained by Dieterle's silver technique. Note the characteristic closed safetypin appearance of some of the so-called Donovan bodies (Pund's method).

granulation tissue, which is soft, beefy-red in appearance and bleeds readily.

2. Approximately 10% of cases involve more typically ulcerative lesions, which erode beneath the skin surface and may have a dry or moist floor. In the latter case membranous exudate covers a floor of fine granulations and the lesions are moderately painful.
3. The remaining cases have an array of presentations some of which are quite bizarre. These cases are frequently misdiagnosed as carcinoma of the penis, and error often discovered only at operation.

Sites Involved.

The genitalia are involved in 90% of cases, the inguinal region in 10%, the anal region in 5-10% and distant sites in 1-5%. Lesions are limited to the genitalia in approximately 80% of cases and to the inguinal region in less than 5%. Unilateral lesions are more common than bilateral ones. In the man, lesions most commonly occur on the prepuce or glans and in the woman, lesions on the labia are the most common. The most common distant sites infected are on the head (mouth, lips, throat, face) but involvement of the liver, thorax and bones[8] has also been reported.

Treatment Features.

Within a few days of commencing treatment, the lesions become paler, less exuberant and less friable. Shrinking of the lesions by peripheral epithelialization is evident after 7 days and total healing, except in grossly advanced cases, usually occurs within 3-5 weeks. Relapse frequently occurs, and this is more common if antibiotic is discontinued before the primary lesion has completely subsided.

Donovan bodies are usually no longer apparent in smears obtained after 5-10 days of treatment. If treatment is ceased at this stage, the lesion often continues to heal but Donovan bodies may reappear within 7-10 days and the lesion may become active again. In other cases, healing continues to complete cure.

Diagnosis

The clinical presentation is highly suggestive of the diagnosis in most cases. However, the diagnosis is readily confirmed by a stained crush preparation from the lesion. The sensitivity of this test is closely related to the manner in which it is performed. A piece of clean granulation tissue from a lesion is spread against the slide to

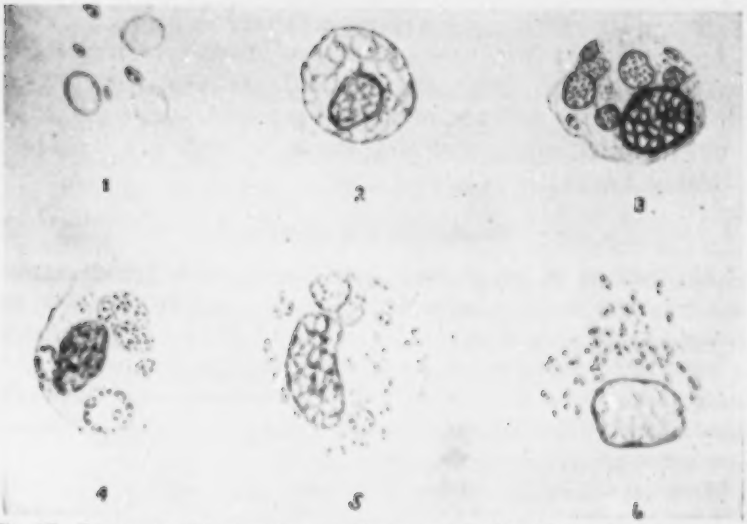

Fig. 15. Camera lucida drawings to illustrate possible life cycle of Donovan bodies (Dienst), reduced from a magnification of 1,500 diameters: (1) Mature extracellular organisms with red blood cells. (2) Large mononuclear endothelial cell showing early invasion with Donovan bodies. (3) Infected cell showing multiplication of immature organisms in cystic spaces. (4) Further multiplication and maturation of organisms in monocyte. (5) Individual organisms becoming mature. (6) Mature encapsulated Donovan bodies escaping from ruptured and disintegrating monocyte.

be examined. The smear obtained is air dried and stained with Wright's or Giemsa's stain.

Donovan bodies appear as clusters of blue- or black-staining organisms with a "safety pin" appearance (from bipolar chomatin condensation) in the cytoplasm of large mononuclear cells. Histological examination of biopsied tissue is a less reliable diagnostic procedure since the pathognomonic Donovan bodies are infrequently seen.

Culture on chick chorioallantoic membrane is not feasible as a routine diagnostic measure.

Treatment

Streptomycin and tetracyclines are often effective but resistance may develop. Ampicillin has proved of limited value.[9,10] Gentamicin (40 mg. twice daily intramuscularly) and chloramphenicol (0.5 gm. every 8 hours orally) are probably the most effective drugs and cure most lesions within 3 weeks.

In any community, it is wise to use tetracyclines (0.5 gm. every 6 hours) as first-line therapy and then change progressively to streptomycin (0.5 gm. twice daily), chloramphenicol and gentamicin if the efficacy of the current antibiotic wanes. If an antibiotic is effective, clinical response to treatment should be evident in 7 days.

Prevention and Control

No method of prophylaxis has been assessed. The disastrous sequelae, such as complete genital erosion or urethral occlusion, are caused solely by delay in seeking treatment. If treated at the time of appearance of the initial subcutaneous nodule, Donovanosis is a benign disease. The primary aim of the control campaign, therefore, should be to encourage the population to seek treatment as soon as they are aware of genital or inguinal lesions.

In areas where the disease is endemic, mass surveys of the total male population, age 15-40, should be conducted yearly until the prevalence falls below 1%.[11] Donovanosis should be diagnosed by inspection and all the steady sex partners of detected cases given epidemiologic treatment.

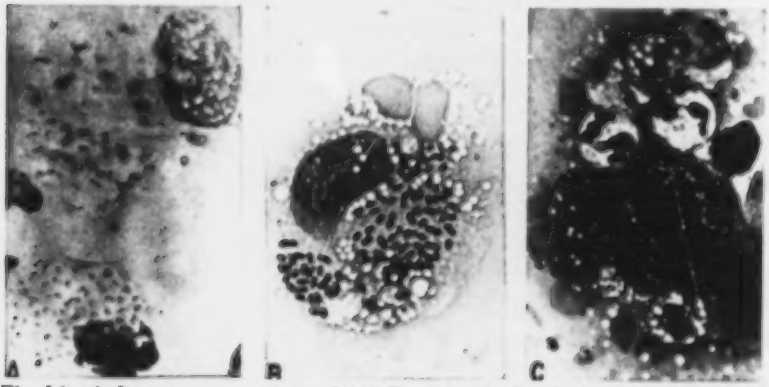

Fig. 16. *A.* Immature nonencapsulated Donovan bodies lying in cytoplasm of mononuclear cells. *B.* Mature encapsulated Donovan bodies within cytoplasm of large mononuclear cell. *C.* Note multiple cytoplasmic cysts filled with Donovan bodies in large mononuclear cell.

References

1. Dodson, R. F., et al.: Donovanosis: a morphologic study, J. Invest. Derm., 62:611, 1974.
2. Anderson, K., Goodpasture, E. W. and DeMonbreun, W. A.: Etiologic consideration of *Donovania granulomatis* cultured in three cases in embryonic yolks, J. Exper. Med., 8:451, 1945.
3. Hart, G.: Psychological and social aspects of venereal disease in Papua New Guinea, Brit. J. Vener. Dis., 51: , 1974.
4. Lal, S. and Nicholas, C.: Epidemiological and clinical features in 165 cases of granuloma inguinale, Brit. J. Vener. Dis., 46:461, 1970.
5. Goldberg, J.: Studies on granuloma inguinale VII. Some epidemiological considerations of the disease, Brit. J. Vener. Dis., 40:140, 1964.
6. Marmell, M.: Donovanosis of the anus in the male. An epidemiologic consideration, Brit. J. Vener. Dis. 34:213, 1958.
7. Zigas, V.: Medicine from the past– A Donovanosis project in Goilala (1951-1954), Papua New Guinea Medical Journal, 14:148, 1971.
8. Kirkpatrick, D.J.: Donovanosis (Granuloma Inguinale); A rare cause of osteolytic bone lesions, Clin. Radiol. 21:101, 1970.
9. Thew, M. A., Swift, J. T. and Heaton, C. L.: Ampicillin in the treatment of granuloma inguinale, J.A.M.A. 210:866, 1969.
10. Davis, C. M.: Granuloma inguinale, a clinical histological and ultrastructural study, J.A.M.A. 211:632, 1970.
11. Vogel, L. C.: Een granuloma-venereum (Donovanosis) – epidemic in Zuid Niew Guinea (1920), *Ned. T. Geneesk.* 109:2425, 1965.

LYMPHOGRANULOMA VENEREUM (LGV)

Synonyms

Climatic bubo; Durand-Nicholas-Favre disease; Frei's disease; LGV; lymphogranuloma inguinale; lymphogranulomatis inguinalis; lymphopathia venereum; poradenitis venerea; poradenitis nostras; tropical bubo.

Definition

Lymphogranuloma venereum (LGV) is a systemic sexually transmitted disease which may be produced by a number of closely related *chlamydia*. Primary inoculation may occur at any anatomic site involved in intimate contact. Regional lymphadenitis develops in the nodes draining this site and the disease disseminates further via the lymphatic system. Progression of the disease may produce chronic buboes, elephantiasis, fistulae and strictures.

History.

Wallace first described LGV in 1833, but a more comprehensive description was provided by Nicholas, Durand and Favre in 1913. Gay-Prieto observed the causative organism in 1927. Frei prepared the original antigen of his skin test in 1925 and Rake, McKee and Shaffer prepared a more specific antigen in 1940.

Infectious agent

LGV may be caused by several related chlamydial organisms.[1] The causative organism has been named *Miyagawanella lymphogranulomatis* in one text.[2]

Chlamydia are small obligate intracellular bacteria which may be divided into subgroup A (those producing iodine-staining inclusions), containing the causative organisms of trachoma, inclusion conjunctivitis (TRIC) and more isolates from LGV, and subgroup B (nonstaining inclusions) which contains the organisms of ornithosis and various animal diseases. Some strains of chlamydia subgroup A are resistant to sulfonamides *in vitro* but all are sensitive to tetracycline. When inoculated intracerebrally into mice the organisms of LGV are lethal whereas TRIC organisms are not.

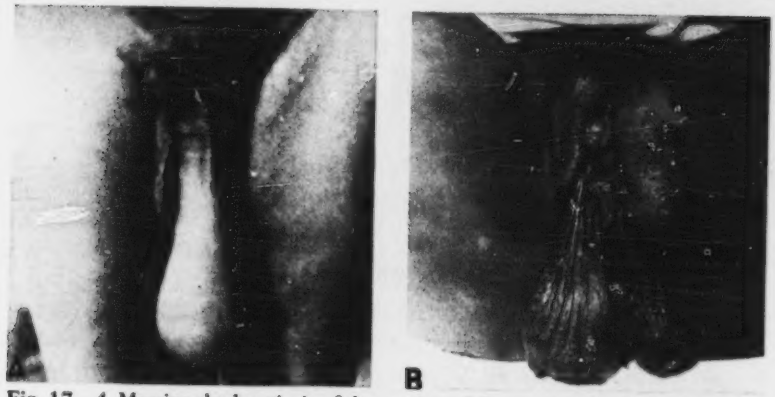

Fig. 17. *A.* Massive elephantiasis of the penis and *B.* massive elephantiasis of the labia minora and majora due to virus of lymphogranuloma venereum.

Immunofluorescence is the preferred method for typing TRIC and LGV strains.[3] Nine antigenic types (types A through I) of TRIC,[4] of which types A-C are mostly ocular and types D-I mostly genital, and three antigenic types (I, II, III) of LGV[5] have been characterized.

The organism is unaffected by freezing; it remains virulent for 24-48 hours at room temperature, for less than 30 minutes at 46°C and is killed in 10 minutes at 56°C.[6]

Immunity

Host response to infection varies greatly. Some patients have mild lymphadenopathy which subsides spontaneously whereas others develop chronic draining fistulae which may persist for years. Relapse after treatment is common; however, proven reinfection has not been reported.

Epidemiology

The disease has a world wide distribution but is more common in tropical or subtropical regions and is now most prevalent in Southeast Asia. Although it has been considered endemic among blacks in the southern United States, its present incidence is unknown. Only 374 cases were reported in this country in Fiscal Year 1974 and 217 of these were in nonwhite males.

Infection is readily transmitted by any form of intimate sexual contact, but the contribution of nonsexual transmission is unknown.

Extragenital infection is epidemiologically important because the disease may remain undetected for a long period after rectal

inoculation, and is rarely suspected at other nongenital sites.

LGV has been described as a cause of some cases of nonspecific urethritis. However, better characterization of chlamydial organisms may reveal that urethral infection is caused by a chlamydia organism not involved in the other lesions of LGV.

Pathology

The initial transient lesion which develops at the site of inoculation may be nodular or vesicular. Lymphangitis of the coronal sulcus and dorsal lymphatics of the penis may occur and bubonules sometimes appear along the inflamed lymphatics.

Infection spreads to the lymph nodes that drain the site of inoculation and usually extends until all glands of the group are involved. After periadenitis develops, the glands become matted to form one conglomerate mass. Abscesses develop in one or more

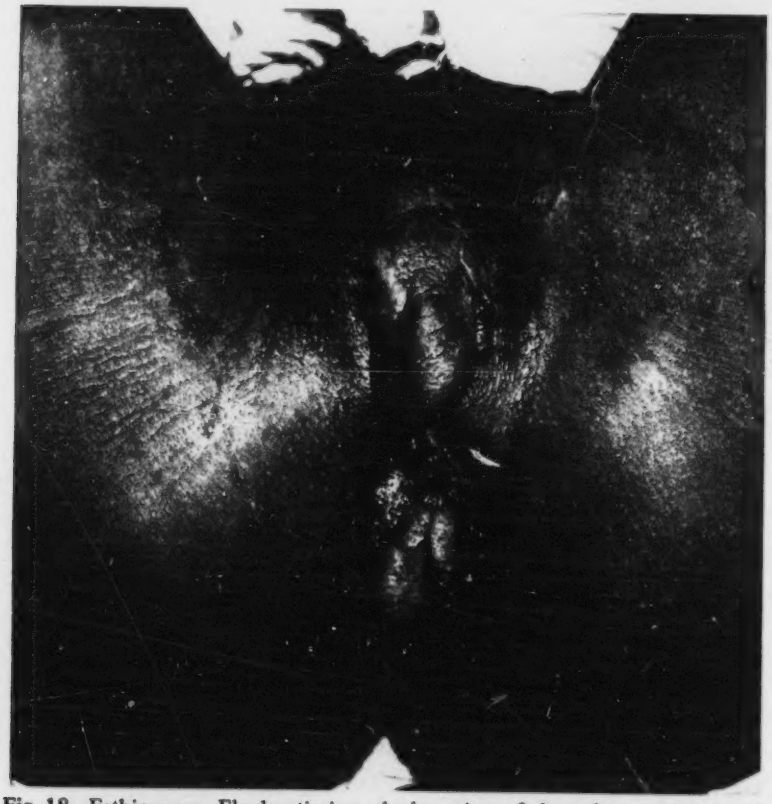

Fig. 18. Esthiomene. Elephantiasis and ulceration of the vulva and lobulated anal growths.

zones and eventually rupture through the skin or other epithelial surfaces to produce draining sinuses or fistulae which characterize the advanced stages of the disease.

The histological changes suggest LGV, but are not pathognomonic. Initially small stellate abscesses are surrounded by histiocytes, in palisadelike arrangement. There may be central caseation necrosis, foreign body giant cells, and a dense inflitrate of plasma cells in later stages.

Symptoms

There are three clinical phases of infection: inoculation and primary lesions, lymphatic dissemination with constitutional symptoms, and late complications. However, any of these phases may be absent or pass unnoticed in any individual case.

A primary sore may appear on the genitalia, rectum, mouth, or less commonly at other sites, 3 days to 3 weeks after infection, but the incubation period is usually 7-12 days. A primary genital lesion is noticed by about 30% of infected heterosexual men but less frequently in women. It is usually a small painless vesicle or superficial nonindurated ulcer and most commonly occurs on the coronal sulcus, prepuce or glans in men, or on the fourchette, vagina or cervix of women. Associated local or regional edema may produce phimosis or swelling of the labia. Rectal inoculation produces bloody anal discharge and tenesmus at first, then mucopurulent discharge, diarrhea and cramps. Simultaneous inoculation into the mouth, genitalia or other regions may occur.[7,8] Oral infection without genital infection in a patient who

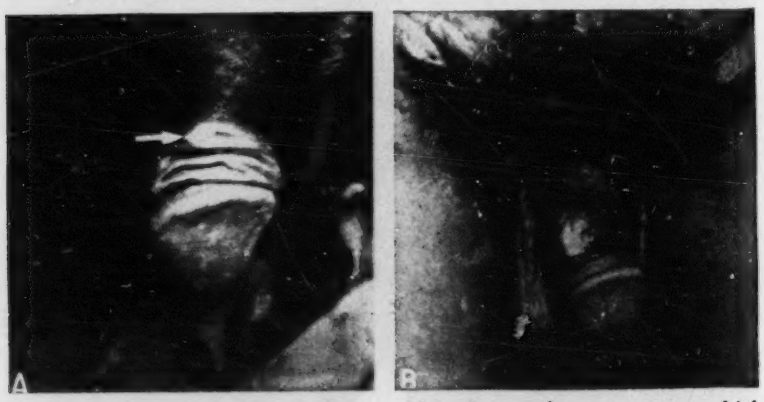

Fig. 19. *A.* Evanescent primary lesion of lymphogranuloma venereum which was followed in 3 weeks by *B.* an ulceration on the shaft of the penis simultaneously with bilateral buboes.

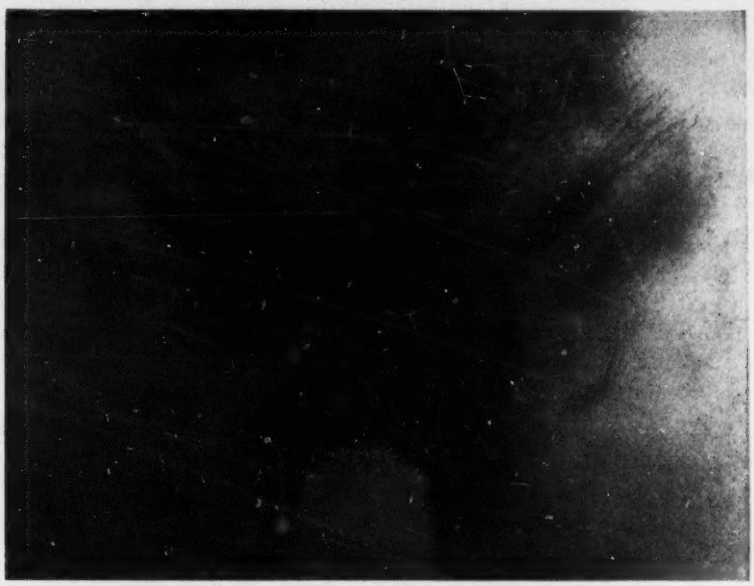

Fig. 20. Typical elongated buboes of lymphogranuloma venereum. The enlargement of the nodes above and below the groin fold is characteristic.

practiced coitus and cunnilingus with all sex partners has been reported.[9]

Primary lesions are followed in 7-30 days by adenopathy of the regional lymph nodes. The superficial inguinal nodes are involved when the primary lesion is on the penis, anal margin, clitoris or upper vulva, but simultaneous involvement of the deep iliac lymph nodes occurs in over 75% of cases. Inoculation in the vagina or cervix produces adenopathy in the deep iliac and anorectal nodes; rectal inoculation produces adenopathy of the deep iliac, perirectal and hypogastric nodes; oral inoculation usually produces submaxillary and cervical adenopathy, but Sheldon[10] has reported cases of supraclavicular and mediastinal lymphadenopathy and pericarditis, after tonsillar inoculation. Conjunctival inoculation produces preauricular and submaxillary adenopathy.

Sensation of stiffness and aching in the groin, followed by swelling of the inguinal region, is the first indication of infection for most patients. As infection spreads to involve all the nodes in the group, they become matted and attached to the overlying skin which may have a characteristic purplish color. Frequently involved, the nodes above and below Poupart's ligament produce "the sign of the groove" – a linear depression in the elongated

inflammatory mass. Inguinal adenopathy is unilateral in about 70% of cases. Adenopathy may subside spontaneously or proceed to the formation of abscesses which rupture to produce chronic draining sinuses or fistulae.

Lymphatic spread is associated with variable constitutional symptoms. Mild fever frequently precedes adenopathy and lasts for several days. In other cases high fever, sweating and rigors occur. Malaise, nausea and vomiting occur,.particularly in those with high fever. Abdominal pain, urinary retention and symptoms of cystitis are common when pelvic nodes are involved. Transitory myalgia and arthralgia are common, whereas erythematous skin lesions occasionally occur. Hepatomegaly, splenomegaly, nephropathy, meningismus and phlebitis have been reported.

Common hematological changes in this phase include: mild anemia, leucocytoses, elevated sedimentation rate, hypolipidemia and hyperglobulinemia.

Complications.

Large polypoid swellings of the vulva, anal margin and rectal mucosa may develop. Elephantiasis of the genitalia is a more serious late complication and may involve the prepuce, penis, scrotum or vulva.

The most severe morbidity, however, results from rectal involvement. Perianal abscess, rectovaginal, rectovesical and ischiorectal fistulae appear as early complications and rectal stricture may develop 1-10 years after infection. Annular bands or funnel-shaped strictures may result from perirectal involvement, but tubular or rubber-hose stenosis is more common and presumably results from rectal inoculation. Bloody mucopurulent discharge, pruritus, tenesmus, and intermittent constipation occur with established stenosis; and painful ileus, distension, complete obstruction, perforation and peritonitis develop in the most advanced stages.

Diagnosis

The causative organism has been grown on chick embryo yolk sac[11] but this method is unsatisfactory for routine diagnosis.

The Frei skin test has been the most widely used test. It becomes positive 12-40 days after appearance of the primary lesion and usually remains so for life. However, it is less than 70% sensitive – frequently negative even in advanced stages of infection.[12] Furthermore, it is nonspecific and frequently reacts in individuals who have been infected with any chlamydial organisms.

The LGV complement-fixation test (LGV-CFT) is 90-95% sensitive and becomes positive earlier than the Frei Test (usually within 1-3 weeks). It is nonspecific, but can be titrated which enhances its value. However, neither the Frei test nor the LGV-CFT is of great value alone and certainly of no value as a screening test.

The immunofluorescence[13] and neutralization tests[14] are specific for LGV but are not widely available and have had limited evaluation.

In the presence of the clinical syndrome, a fourfold rise in titer of the complement-fixation test is diagnostic. However, this test has usually risen to a stable titer by the time most patients present for diagnosis, and may not decline significantly for several months.

Bedson[15] suggested that a positive Frei test and a CFT titer of 1:16 or higher in a patient with clinical signs of LGV was good evidence of the disease, whereas Douglas[16] considered that a CFT titer of 1:80 or higher indicates active disease. Certainly, treatment should be initiated in patients with the clinical syndrome who have a CFT titer of 1:64 or higher.

Treatment

Early antibiotic therapy is important in reducing the morbidity of the disease and treatment should never be withheld while awaiting laboratory proof of infection. Oral tetracycline (0.5 gm. every 6 hours) is recommended and should be administered for at least 3 weeks. If pregnancy or idiosyncrasy precludes tetracycline,

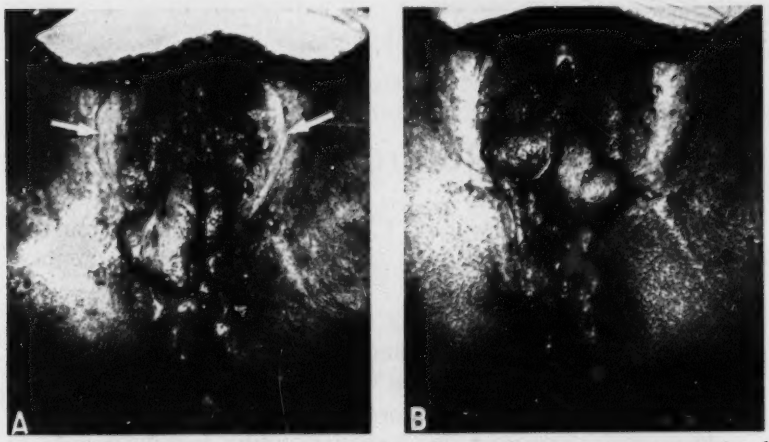

Fig. 21. *A.* Obstinate ulceration of lymphogranuloma venereum associated with elephantiasis of the vulva and lymphorroids. *B.* Note healing of ulceration after course of aureomycin, with little change in the lesions due to lymphoid stasis.

sulfisoxazole[17] (4 gm. initially and 0.5 gm. every 6 hours) should be used.

Fluctuant lymph nodes should be aspirated, but surgical intervention should otherwise be minimized. Although discrete polypoid masses may be excised, surgical removal of lymph nodes or extensive areas of lymphedematous tissue may worsen lymphedema or elephantiasis. Rectal stricture should be managed by dilatation at 2-week intervals. Colostomy should be reserved for the most refractory cases, for which conservative management fails. Surgery is contraindicated during active disease and should be covered by antibiotic therapy from 2 weeks before until 2 weeks after operation.

LGV is characterized by remissions and exacerbations, and thorough surveillance is important. Full clinical assessment and LGV-CFT titer should be determined every 3 months for at least one year after cure. Antibiotic therapy should begin again as soon as there is evidence of reactivation.

Prevention and Control

There are no proven preventive or control measures. The condom probably provides some protection against genital-genital transmission but will have little impact on transmission between other sites.

Since the morbidity is closely related to duration of illness, physician and public education may reduce this impact by favoring early treatment. The located sexual partners of infected persons should receive epidemiologic treatment.

References

1. Schachter, J. and Meyer, K. F.: Lymphogranuloma Venereum. II. Characterization of some recently isolated strains, J. Bact. 99:636, 1969.
2. Breed, R. S., Murray, E. G. D. and Smith, N. R. editors: Bergey's Manual of determinative bacteriology, 7th Edition, Baltimore, 1957, Williams and Wilkins.
3. Philip, R. N. et al.: Fluorescent antibody responses to chlamydial infection in patients with lymphogranuloma venereum and urethritis, J. Immunol. 112:2126, 1974.
4. Wang, S. P. in Nichol, R. C. editor: Trachoma and related disorders. Amsterdam, 1971, Excerpta Medica.

5. Wang, S. P., Grayston, J. T. and Gale, J. L.: Three new immunologic types of trachoma-inclusion conjunctivitis organisms, J. Immunol. 110:873, 1973.
6. Coutts, W. E.: Lymphogranuloma venereum, a general review, Bull. WHO 2:545, 1950.
7. Costello, M. J. and Cohen, J. A.: Lymphogranuloma venereum affecting simultaneously cervical and inguinal lymphatic glands, a report of a case, Arch. Derm. (Chic.) 41:557, 1940.
8. Curth, H.: Extragenital infection with the virus of lymphogranuloma inguinale, Arch. Derm. (Chic.) 28:377, 1933.
9. Andrada, M. T., Dhar, J. K. and Wilde, H.: Oral lymphogranuloma venereum and cervical lymphadenopathy, Milit. Med. 139:99, 1974.
10. Sheldon, W. H. et al.: Lymphogranuloma venereum of supraclavicular lymph nodes with mediastinal lymphadenopathy and pericarditis, Amer. J. Med. 5:320, 1948.
11. Rake, G. W., McKee, C. M. and Shaffer, M. F.: Agent of lymphogranuloma venereum in the yolk sac of the developing chick embryo. Proc. Soc. Exper. Biol. and Med. 43:332, 1940.
12. Schachter, J. et al.: Lymphogranuloma venereum. I. Comparison of the Frei Test, complement fixation test, and isolation of the agent, J. Infect. Dis. 120:372, 1969.
13. Nichol, R. L. and McComb, D. E.: Serologic strain differentiation in trachoma, J. Exp. Med. 120:639, 1964
14. Graham, D. M. and Layton, J. E.: The induction of group antibody in rabbits inoculated with trachoma agents and demonstration of strain-specific neutralizing antibody in sera, in Nichols, R. L. editor Trachoma and Related Disorders, Amsterdam, 1971, Excerpta Medica
15. Bedson, S. P. et al. Laboratory diagnosis of lymphogranuloma venereum, J. Clin. Path. 2:241, 1949.
16. Douglas, C. P. Lymphogranuloma venereum and granuloma inguinale of the vulva, J. Obstet. Gynaec. Brit. Comm. 69:871, 1962.
17. Abrams, A. J.: Lymphogranuloma venereum, J.A.M.A. 205:199, 1968.

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